

CGATGTCTGCACAAGGCTGTCACTCAGGTGGCAGTGGCTGACACGTGGCCGGGCAGCTCTGC
TGCTGCGGCGCGAAGTCGAGAGGCGGCGGGTCCGTGGCGCGCTCGCATTTGCTCCGAGGC
TCCGAGCGGCGATACGGGCGGGCGCCGACGGCAGGGTCTCCATGCCCCGCGCTGGGGCGGGC
CGCTGATGGAGCGCGCCACCCGGCCCGGGCCGCGCGCTGCTGCTTCTGTTCTTGCTG
CTGGGCTGCGCGGCGGGGATCTCTGCGGTGCGCGCCCGCCGAGTTTGCTTGCTCCCGCGTC
GGAGACAGTGTGTTGGCTTAGGGGCAGCGGCCGCCCCGACTTCGGCCGCGCGGGTGCTGCGG
TGGCAACGCGCCGAAGTGACCGTGGAGGACGCCGAGGCATTGCCGGCTGCCGCTGGCGAACCG
GAGTCACGCGCGACGGAGCCCGATGACGACGTGGAAGTGCAGGCTCGCGGCAGGTCCTTGGT
AATCATCAGCACTTTAGATGGACGAATCGCTGCACTGGATGCCGAGAATGATGGGAAAAAGC
AGTGGGATTTGGACGTGGGGTCTGGTTCTTGGTTTCATCTAGCCTCAGCAAGCCAGAGGTG
TTTGGGAACAAGATGATCATCCCCCTCCCTGGATGGAGACCTCTTCCAGTGGGACCGGGACCG
AGAGAGCATGGAGGCCGTCCCCCTCACGGTGGAGTCCCTGCTCGAATCTTCTTACAAGTTTG
GAGATGATGTTGTTCTGGTTGGAGGGAAATCTCTGATTACATACGGAAGTCACTGCTTACAGT
GGAAAGCTGAGGTATATCTGTTCTGCCTTGGGATGTCGCGCATGGGATAGTGATGAAATGGA
AGAAGAGGAAGACATCTTGCTTCTGCAGCGTACGCAGAAGACTGTGCGAGCTGTCGGGCCCTC
GAAGCGGCAGTGAGAAGTGAATTTAGTGTGGCCACTTTGAACTTCGGTATATTCAGAC
ATGGAAACTAGAGCCGATTCAATTGAAAGCACCTTTAAACCGGGTGGAAACAAAGAAGACTC
TAAAATTATTTAGATGTGGAAGAACAAGAAGCCACCATGCTGGACACAGTGATAAAAGTTT
CCGTTGCTGATTGGAAGGTATGGCGTTTAGTAGGAAGGAGGCCCTGGAATGGGAGTAC
CAGTTTGTACTCCCATCGCGTCCGCTGGCTGGTGGAGGATGGCAAGGTATCCCCATCAG
CCTGTTGATGATACAAGTTACACAGCCAGCGAAGAAGCCTTGGGAGACGAAGAAGACATTG
TAGAGGCTGCTCGGGGAGCCACAGAGAAGCGGTGTAAGGATGTACAGAGGCCAGCTG
TACCTGCAGTCGTCCGTGAGGTCTCAGAAAAGTTCCCTACAAGCCAAAGGCCTTGGAGTC
TGTAATGGCGAAAATGCAATTATTCCTCTGCCGACGATCAAATGGAAGCCCTTAATCCATT
CTCCTTCTAGGACTCCTGTCTTGGTTGGTCTGATGAATTTGACAAATGTCTAAGTAATGAT
AAGTATTTCCACGAAGAATACAGTAATGGTGCACCTTCAATCCTCCAGTATCCATACGATAA
CGGTTACTATCTGCCATACTACAAGAGAGAAAGGAATAAGCGGAGCACGCAGATCACAGTCA
GGTTCCTGGACAGCCCCACTACAGCAAGAACATCCGCAAGAAGGACCCTATCCTCCTGCTG
CACTGGTGAAGGAGATATTCGGGACGATCCTGCTTTGCATCGTAGCCACGACCTTCATCGT
GCGCAGGCTTTTCCATCCTCAGCCCCACAGGCAGCGGAAGGAGTCTGAAACTCAGTGCCAGA
CTGAAAGTAAATACGACTCCGTGAGTGCCGATGTGAGTACACAGCTGGAATGACATGAAG
TACTCAGGATACGTATCCCGATATCTAACAGATTTTGAGCCAATTCAGTGCATGGGTGCTGG
TGGCTTTGGCGTTGTCTTTGAAGCTAAAAACAAAGTAGATGACTGCAATTACGCTATCAAGA
GGATCCGGCTCCCCAACAGGGAGTTGGCACGGGAGAAGGTAATGCGGGAAGTTAAAGCCTTG
GCTAAGCTGGAACACCCAGGCATTGTGAGGTATTTCAACGCCTGGCTGGAAACCCACCAGA
GAAGTGGCAAGAAGAGATGGATGAGATCTGGCTCAAAGACGAAAGCACAGACTGGCCGCTCA
GCTCCCCTAGCCCGATGGATGCCCCATCTGTTAAGATCCGAAGGATGGATCCYTTCTCTACA
AAAGAGCAGATCGAAGTCATAGCTCCTTCTCCTGAAAGAAGTGGTCTTTCTCGGTGGGCAT
TTCTGTGGCCAGACAAGCTCATCGGAGAGCCAGTTCTCTCCCCTGGAGTTCTCAGGGACAG
ACTGCGGAGACAACAGTGACTCAGCGGACGCAGCCTACAACCTCCAGGACAGTTGCCTGACG
GACTGCGAGGACGTGGAAGATGGCACCGTGGACGGCAATGACGAGGGACACTCCTTTGAACT
TTGTCCGTCCGAAGCTTCTCCCTATACCCGGTCTAGGGAAGGAACGTCTCTCCATAGTGT
TTGAGGACTCTGGCTGCGGCAACGCGTCCAGTAAGGAGGAGCCAGAGGGAACCGGCTGCAT
GATGGCAACCATTATGTTAATAAGCTAACTGATCTCAAGTGCTCCAGCAGCAGGTCTTCTTC
AAGAACACTGTGGGCCAGCTCCAGCCCAGCTCCCCCAAGGTGTATCTGTGAAGCCACCCT
TGTCTACCTCCCCTACCAGGCCAACCCTCTAAGCTTGGATTTACCAACATTGAGATGCAG

FIGURE 1A(1)

1000593 11091

10005983 "110701"

CTGTGCAGGAAGGAGAACCTCAAAGACTGGATGAACCGGCGCTGCAGCTTGGAGGACCGGGA
GCACGGCGTGTGCCTGCACATCTTCCTGCAGATCGCAGAGGCAGTGGAGTTCCTGCACAGCA
AGGGACTCATGCACAGGGACCTCAAGCCTTCCAACATATTCTTCACAATGGATGATGTGGTC
AAGGTTGGGGACTTTGGACTGGTGAATGCTATGGACCAAGATGAAGAAGAGCAGACTGTTCT
GACTCCAATGCCAGCCTATGCTACGCACACGGGACAAGTAGGGACCAAGCTATACATGAGCC
CAGAGCAGATTGATGGAACAACACTACTCCCATAAAGTGGACATCTTCTCTTTAGGCTTGATT
CTGTTTGAACCTCCTTACCCATTGAGCAGCCAGATGGAACGAGTCCGGATTTTAACTGATGT
CAGAAATCTCAAGTTTCCTCTACTGTTCACTCAGAAATATCCCCAAGAGCATATGATGGTTC
AAGACATGCTCTCTCCATCCCCACGGAGCGGCTGAAGCCACAGACATCATTGAAAATGCC
ATATTTGAGAACTTGGAGTTTCCCGGGAACCGGTTCTGAGACAGCGGTCCCGCTCCATGAG
TTCATCTGGAACAAAACATTCCAGACAGCCCAGCTGCTCGTACAGCCCACTGCCTGGCAACT
AGCCCTCAGCTGCCCTCGAAGGTGGCAGAGCAGGCACCCCTGAGGAACATGGCTCTCCACAGC
GGTGGACTCAGATTTTATGCTTTGATCAGTTGGACTCGGGACCAATTTTCTAAGTCAGACT
GGATCACGGGCCTAACCCAGTTTGATCTTAACTGAACTTCAAGGAAAGGGCTGTGTAAAGGA
CACATGAACTTGTTGCTTGTCGGTGTCCCAAGACTAGCTGGTCAGCTTAGAACCTTCACTTT
TCACCAGGCGGTAGAAGAGATCCTCAAATGGTCTGAACTGGAAATGTCTTTAAAGCACAAAA
GTGTAAAAGACCCTCTCACATGGGAACACTACATGTTCTAGAAACGTGCTTTCTAGAGATACAA
GGGTGATTTTGGAAAGTGGTTGTTATAAAGCTGACTTCATTTTTTTCCCTGGTGAGCCGTGAC
CCATCTGCACTAATTTGCAAGGCACATAGCACAAAGCTGGGTCGCCATTTATGTCGGTAGTGT
CATAGTCTGCAGCAGTGAATAGCGTCATTCTTCAGGTGGTCTAGGGAGCGCGAAAAGCTTTT
TTGTACTTTTTACCTCCAATAATGGGAAAATGAAGCTTTTAGGTATTGGTCAAAAGATCTGA
TTTGAGAGTTTGGGTTTTTTTTTTAAGTGCAGTAGGAAATGGATTATCTATTACAACATAAC
TTCTTCAATTATGGAATTTTTATCCTAGTAGAATTCTGTCTTAAATGTAATACTACAAGTGG
GTACATTCCCCCAAACCTGATTATAGATAAGTTAATCATCTCAACTTGCTAACATGTTTTCA
TTTTTCCTGTAAATACGTTTATTTTTTATTTATAAAAATTCTGAAATCAATCCATTGGGTT
GGTGGTGTACAGAACGCACGTAAGTGTGATAACTATTATGACTTCTTTCAAGTCTAAATGAT
TTAATAAAAAAATTTTAAATTAATAAAAAAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:1)

FIGURE 1A(2)

1005993 110701

MERATRPGPRALLLLLFLLLGCAAGISAVAPARSLLAPASETVFGLGAAAAPTSAARVPAVA
 TAEVTVEDAEALPAAAGEPESRATEPDDDVELRPRGRSLVIISTLDGRIAALDAENDGKKQW
 DLDVSGSLVSSSLSKPEVFGNKMIIPSLDGDLFQWDRDRESMEAVPFTVESLLESSYKFGD
 DVVLVGKSLITYGLSAYSGKLRYSALGCRRWDSDEMEEEEDILLQRTQKTVRAVGPRS
 GSEKWNFSVGHFELRYIPDMETRAGFIESTFKPGNKEDSKII SDVEEQEATMLDTVIVKSV
 ADWKVMAFSRKGRLEWEYQFCTPIASAWLVRDGKVIPI SLFDDTSYTASEEALGDEEDIVE
 AARGATENS VYLGMYRGQLYLQSSVRVSEKFPTSPKALESVNGENAI I PLPTIKWKPLIHSP
 SRTPVLVGSDEFDKCLSN DKYSHEEYSNGALSILQYPYDNGYYLPYYKRERNKRSTQITVRF
 LDSPHYSKNIRKKDPILLHWWKEIFGTILLCIVATTFIVRRLFHPQPHRQRKESETQCQTE
 SKYDSVSADVSDNSWNDMKYSGYVSRYLTDFEPIQCMGRGGFGVVFEAKNKVDDCN YAIKRI
 RLPNRELAREKVMREVKALAKLEHPGIVRYFNAWLETPEKWQEEMDEIWLKDESTDWPLSS
 PSPMDAPSVKIRRMDFSTKEQIEVIAPSPERSRSFSGISCGQTSSSESQFSPLEFSGTDC
 GDNSDSADAAYNLQDSCLTDCEDVEDGTVDGNDEGHSFELCPSEASPYTRSREGTSSSIVFE
 DSGCGNASSKEEPRGNRLHDGNHYVNKLTDLKCSSSRSSSEATTLSTSPTRPTTSLDFTKN
 TVGQLQPSSPKVYLYIQMQLCRKENLKDWMNRRCSLEDREHGVCLHIFLQIAEAVEFLHSGK
 LMHRDLKPSNIFFTMDDVVKVGDFGLVTAMDQDEEEQTVLTPMPAYATHTGQVGTKLYMSPE
 QIHGNNYSHKVDIFSLGLILFELLYPFSTQMVRILTDVRNLKFPLLFTQKYPQEHMMVQD
 MLSPSPTERPEATDIIENAI FENLEFPGKTVLRQSRSMSSSGTKHSRQPSCSYSPLPGN
 (SEQ ID NO:2)

FIGURE 1B

underlined = deleted in targeting construct

[] = sequence flanking Neo insert in targeting construct

CGATGTCTGCACAAGGCTGTCACTCAGGTGGCAGTGGCTGACACGTGGCCGGGCAGCTCT
GCTGCTGCGGCGCGAAGTCGAGAGGCGGCGGGTCCGTGGCGCGCTCGCATTGCTCCG
AGGCTCCGAGCGGCGATACGGGCGGGCGCGACGGCAGGTCTCCATGCCCCGCGTGGG
GCGGGCCGCTGATGGAGCGCGCCACCCGGCCCGGGCCGCGCGCTGCTGCTTCTGT
TCCTGCTGCTGGGCTGCGCGGCGGGGATCTCTGCGGTGCGCGCCCGCCGAGTTTGTCTG
CTCCCGCGTGGAGACAGTGTGTTGGCTTAGGGGACGCGCCCGCCGACTTCGGCCGCGC
GGGTGCTGCGGTGGCAACGGCCGAAGTGACCGTGGAGGACGCGGAGGCATTGCCGGCTG
CCGTGGCGAACCAGAGTCACGCGCGACGGAGCCGATGACGACGTGGAAGTGGCGCCTC
GCGGCAGGTCCCTTGTAATCATCAGCACTTTAGATGGACGAATCGCTGCACTGGATGCCG
AGAATGATGGGAAAAAGCAGTGGGATTTGGACGTGGGTCTGGTTCCTTGGTTTCTCTA
GCCTCAGCAAGCCAGAGGTGTTTGGGAACAAGATGATCATCCCTCCCTGGATGGAGACC
TCTTCCAGTGGGACCGGGACCGAGAGCATGGAGGCCCTCCCTTACGGTGGAGTCCC
TGCTCGAATCTTCTACAAGTTTGGAGATGATGTTGTTCTGGTTGGAGGGAAATCTCTGA
TTACATACGGACTCAGTGCTTACAGTGGAAGCTGAGGTATATCTGTTCTGCCTTGGGAT
GTCGCCGATGGGATAGTGATGAAATGGAAGAAGAGGAAGACATCTGCTTCTGCAGCGTA
CGCAGAAGACTGTGCGAGCTGTGCGGCCTCGAAGCGGCAGTGAGAAGTGAATTTCACTG
TTGGCCACTTTGAACCTTCGGTATATTCCAGACATGGAAGTGAAGCCGATTTCATGAAA
GCACCTTTAAACCGGTGGAACAAAGAAGACTCTAAAATTATTCAGATGTGGAAGAAC
AAGAAGCCACCATGCTGGACACAGTGATAAAAGTTTCCGTTGCTGATTGGAAGTCAATGG
CGTTTAGTAGGAAGGGAGGCCCTGGAATGGGAGTACCAGTTTGTACTCCCATCGCGT
CCGCTGGCTGGTGAGGGATGGCAAGTTCATCCCATCAGCCTGTTTGATGATACAAGTT
ACACAGCCAGCGAAGAAGCCTTGGGAGACGAAGAAGACATTGTAGAGGCTGCTCGGGGAG
CCACAGAGAACAGCGTGTACTTAGGGATGTACAGAGGCCAGCTGTACCTGCAGTCCGCG
TCAGGTCTCAGAAAAGTTCCCTACAAGCCCAAAGGCCTTGGAGTCTGTAAATGGCGAAA
ATGCAATTATTCCTCTGCCGACGATCAAAATGGAAGCCCTTAATCCATTCTCCTTCTAGGA
CTCCTGTCTTGGTTGGGTCTGATGAATTTGACAAATGTCTAAGTAATGATAAGTATTCCC
ACGAAGAATACAGTAATGGTGCATTTCAATCCTCCAGTATCCATACGATAACGGTTACT
ATCTGCCATACTACAAGAGAGAAAGGAATAAGCGGAGCACGCAGATCACAGTCAGGTTCC
TGGACAGCCCCACTACAGCAAGAACAATCCGCAAGAAGGACCCTATCCTCCTGCTGCACT
GGTGAAGGAGATATTCCGGACGATCCTGCTTTGCATCGTAGCCACGACCTTCATCGTGC
GCAGGCTTTTCCATCCTCAGCCCCACAGGCAGCGGAAGGAGTCTGAAACTCAGTGCCAGA
CTGAAAGTAAATACGACTCCGTGAGTGCCGATGTCACTGACAACAGCTGGAATGACATGA
AGTACTCAGGATACGTATCCCGATATCTAACAGATTTTGAAGCAATTCAGTGCATGGGTC
GTGGTGGCTTTGGCGTTGTCTTTGAAGCTAAAAACAAAGTAGATGACTGCAATTACGCTA
TCAAGAGGATCCGGCTCCCCAACAGGGAGTTGGCACGGGAGAAGGTAATGCGGGAAGTTA
AAGCCTTGGCTAAGCTGGAACACCCAGGCATTGTGAGGTATTTCAACGCCTGGCTGGAAA
CCCCACCAGAGAAGTGGCAAGAAGAGATGGATGAGATCTGGCTCAAAGACGAAAGCACAG
ACTGGCCGCTCAGTCCCCCTAGCCCGATGGATGCCCCATCTGTTAAGATCCGAAGGATGG
ATCCYTTCTCTACAAAAGAGCAGATCGAAGTCATAGCTCCTTCTCCTGAAAGAAGTCCGT
CTTTCTCGGTGGGCATTTCTGTGGCCAGACAAGCTCATCGGAGAGCCAGTTCTCTCCCC
TGGAGTTCTCAGGGACAGACTGCGGAGACAACAGTGAAGTCAAGCGGACGCGCCTACAACC
TCCAGGACAGTTGCTGACGGACTGCGAGGACGTGGAAGATGGACCGTGGACGGAATG
ACGAGGGACACTCCTTTGAACCTTTGTCCGTCCGAAGCTTCTCCC [TATACCGGTCTAGG

FIGURE 2A(1)

10005983 " 110701

10005983-110701

GAAGGAACGTCTCTCCATAGTGTGAGGACTCTGGCTGCGGCAACGCGTCCAGTAAG
GAGGAGCCCAGAGGGAACCGGCTGCATGATGGCAACCATTATGTTAATAAGCTAACTGAT
CTCAAGTCTCTCCAGCAGCAGGTCTTCTTCAGAAGCCACCACCTTGTCTACCTCCCCCTACC
AGGCCAACCTCTAAGCTTGGATTTCACCAAGAACAACCTGTGGGCCAGCTCCAGCCCAGC
TCCCCCAAGGTGTATCTGTACATTAGATGCAGCTGTGCAGGAAGGAGAACCTC] AAAGA
CTGGATGAACCGCGCTGCAGCTTGGAGGACCGGAGCACGGCGTGTGCCTGCACATCTT
CCTGCAGATCGCAGGCGAGTGGAGTTCCTGCAC [AGCAAGGGACTCATGCACAGGGACC
TCAAG] CCTTCCAAATATTTCTTCAATGGATGATGTGGTCAAGGTTGGGACTTTGGA
CTGGTGAAGTGTATGACCAAGATGAAGAAGAGCAGACTGTTCTGACTCCAATGCCAGCC
TATGCTACGCACACGGGACAAGTAGGGACCAAGCTATACATGAGCCCAGAGCAGATTCTAT
GGAAACAACCTACTCCCATAAAGTGGACATCTTCTCTTAGGCTTGATTCTGTTTGAACCTC
CTCTACCCATTACGACCCCGATGGAACGAGTCCGATTCTTAACTGATGTCAGAAATCTC
AAGTTTCTCTACTGTTTCTCAGAAATATCCCCAAGAGCATATGATGGTTCAAGACATG
CTCTCTCCATCCCCCAGGAGCGCCTGAAGCCACAGACATCATTGAAAATGCCATATTT
GAGAAGTGGAGTTTCCCGGGAAAACGGTTCTGAGACAGCGGTCCCGCTCCATGAGTTCA
TCTGGAACAAAACATTCCAGACAGCCAGCTGCTCGTACAGCCCACTGCCTGGCAACTAG
CCCTCAGCTGCCCTCGAAGGTGGCAGAGCAGGCACCCTGAGGAACATGGCTCTCCACAGC
GGTGGACTCAGATTTTATGCTTTGATCACTTGGACTCGGGACCAATTTTTCTAAGTCAGA
CTGGATCACGGGCCTAACCAGTTTGTATCTTAACTGAACTTCAAGGAAAGGGCTGTGTAA
AGGACACATGAACCTTGTGCTTGTGCGGTGTCTCAAGACTAGCTGGTCAGCTTAGAACCTT
CACTTTTACCAGGCGGTAGAAGAGATCTCAATGGTCTGAACTGGAAATGTCTTTAAA
GCACAAAAGTGTAAGAGACCTCTCACATGGGAAATACATGTTCTAGAAACGTGCTTTCT
AGAGATAACAAGGGTGATTTTGGAAAGTGGTTGTTATAAGCTGACTTCATTTTTTCCCTG
GTGAGCCGTGACCCATCTGCACTAATTTGCAAGGCACATAGCACAAGCTGGGTGCGCCATT
TATGTCGGTAGTGTATAGTCTGCAGCAGTGAATAGCGTCATTCTTCAGGTGGTCTAGGG
AGCGCGAAAAGCTTTTTTGTACTTTTTTACCTCCAATAATGGGAAAATGAAGCTTTAGGT
ATTGGTCAAAAGATCTGATTTGAGAGTTTTGGGTTTTTTTTTAAGTGCAGTAGGAAATG
GATTATCTATTACAACCTAATTCTTCAATTATGGAATTTTATCCTAGTAGAATTCTGTC
TTAAATGTAATACTACAAGTGGGTACATTCCCCAACTGATTATAGATAAGTTTAATCA
TCTCAACTTGCTAACATGTTTTTCATTTTTCTGTAAATACGTTTATTTTTTATTATAAA
AATTCTGAAATCAATCCATTTGGGTTGGTGGTGTACAGAACGCACGTAAGTGTGATAACT
ATTATGACTTCTTTCAAGTCTAAATGATTTAATAAAAAAATTTAAATAAAAA
AAAAAAAAAAAAA

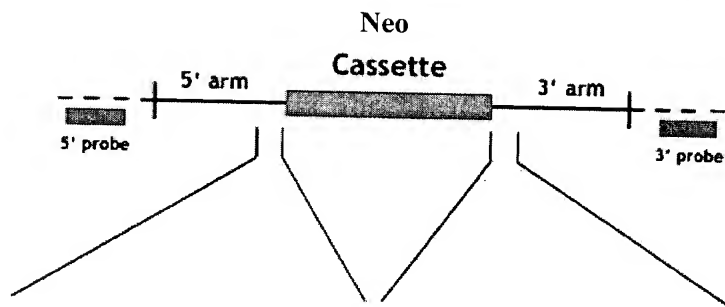
FIGURE 2A(2)

Gene Sequence
Structure *

2874 bp

Sequence Deleted

2972 bp

Size of full-length
cDNA: 4510 bpTargeting Vector*
(genomic sequence)Arm Length:
5': 2.4 kb
3': 1.3 kb

———— Targeting Vector
 - - - - Endogenous Locus

* Not drawn to scale

5' >ACCATTATGTTAATAAGCTAA
 CTGATCTCAAGTGCTCCAGCAGCA
 GGTCTTCTTCAGAAGCCACCACCT
 TGTCTACCTCCCCTACCAGGCCAA
 CCACTCTAAGCTTGGATTTCACCA
 AGAACACTGTGGGCCAGCTCCAGC
 CCAGCTCCCCAAGGTGTATCTGT
 ACATTGAGATGCAGCTGTGCAGGA
 AGGAGAACCTC<3' (SEQ ID
 NO: 3)

5' >AGCAAGGGACTCATGCACGGG
 ACCTCAAGGTCTGTAGCCAGAGGC
 GGCCACGCCGGGCTTTGGGTGTGC
 CCTGGGGTTCAGAGCAGAGGTCGG
 GGAAGGAAGCAGGGAAGGAAGAAG
 TCTCATATGTGAAAGGCTCAGGCA
 GACTGTGCATCTTCCTTTACGGCC
 TGTTTATTTTGTCTTACTGTAAA
 CACTGTTTCCA<3' (SEQ ID
 NO: 4)

FIGURE 2B

Phenotypic Data Summary - Metrazol

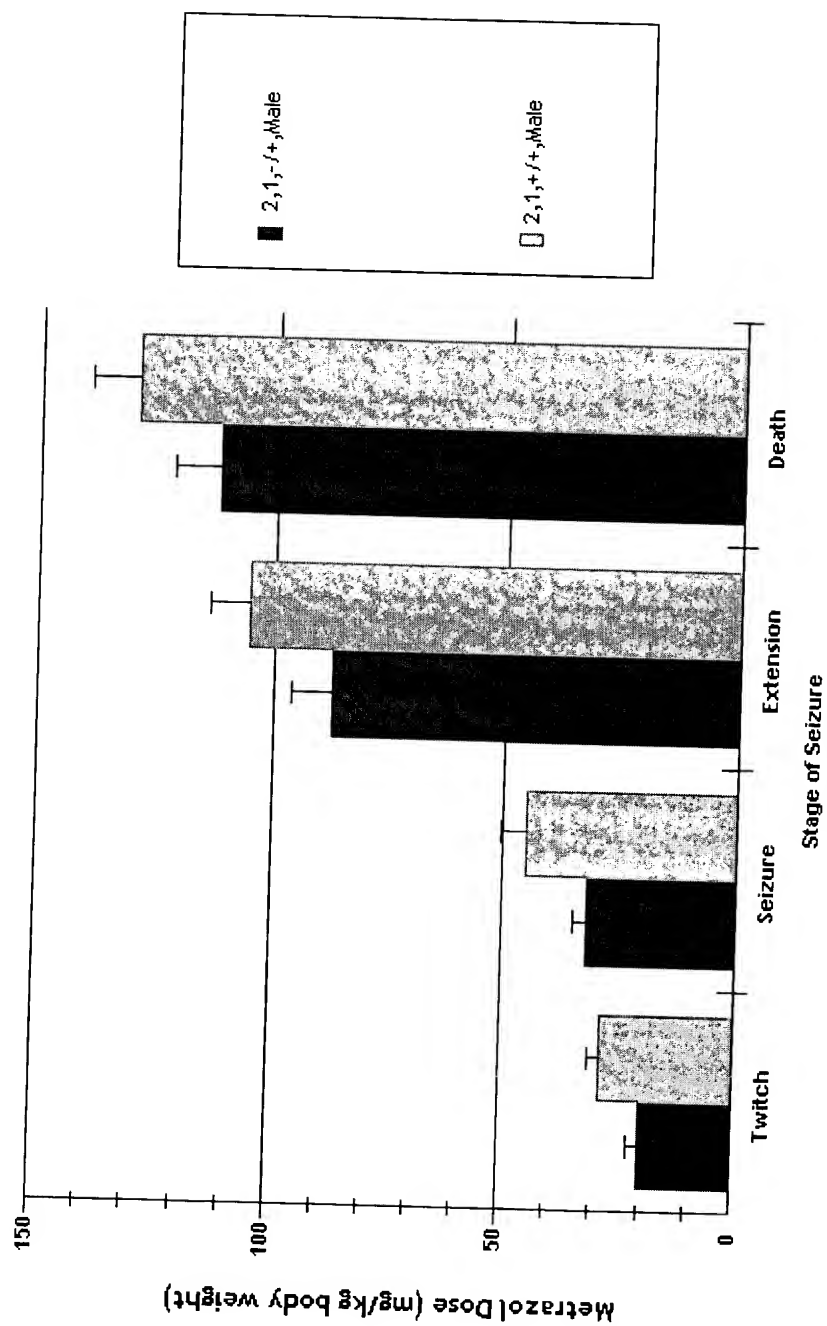


FIGURE 3